(a) a sustained release layer, comprising:

(i) from about 5 to about 70% by weight of a water-soluble polymer;

(ii) from about 15 to about 95% by weight of a first pharmaceutically active agent; and

(iii) up to about 15% by weight of a fatty acid; and

(b) a fast release layer, comprising:

(i) from about 0.5 to about 15% by weight of a matrix forming agent; and

(ii) from about 85 to about 99.5% by weight of a second pharmaceutically active agent.

Q2 Cont

REMARKS

This Amendment is respectfully submitted in response to the Office Action rendered August 1, 2001. It is timely in view of the Petition for Extension of Time submitted concurrently herewith.

Claim 1 has been amended to clarify the language of the claim with respect to the compositions of applicants' invention which are freeze-dried products. Basis for this amendment can be found in the Specification at page 9, line. 22 et seq.

The foregoing new claims find basis in the Specification as follows: claim 56 finds basis in the Specification at page 9, line 22 et seq. and in original claim 1. New claim 57 finds basis in the Specification at page 8, line 19. New claim 58 finds basis in the Specification at page 7, lines 10-11. New claim 59 finds basis in the Specification in original claim 2. New claim 60 finds basis in the Specification in original claim 7. New claim 61 finds basis in the Specification, page 5, lines 3-15. New claim 62 finds basis in the Specification at page 5, lines 10-11. New claim 63 finds basis in the Specification at page 5, line 28 through page 6, line 5. New claim 64 finds basis in the Specification at page 6, lines 17-23. New claim 65 finds basis in the Specification in original claims 1-6, 27 and 38. New claim 66 finds basis in the Specification at page 7, lines 23-24, at page 5, lines 3-15 and at page 6, lines 17-23. No new matter has been added to the Specification.

The compositions of applicants' invention relate to pharmaceutical treatment compositions containing a fast release layer and a sustained release layer. The compositions provide fast and sustained, or controlled, release of a pharmaceutically active agent for at least six hours and preferably for at least 1 to 3 days. The composition is particularly useful

as a vaginal insert for treatment of vaginal diseases without multi-dosing. The compositions of applicants' invention are particularly well-suited for freeze-drying and, in a preferred embodiment, are formed by freeze-drying.

The Office Action of August 1, 2001 confirmed the finality of the restriction requirement. Further, it rejected claim 27 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Office Action indicates that the term "vegetable protein derivatives" in claim 27, line 2 is vague and indefinite. Applicants respectfully request reconsideration of this rejection. The term "vegetable protein derivatives" is amply described in the text of the Specification at page 5, line 29 through page 6, line 1. Reconsideration of this rejection is respectfully sought.

Claims 1, 2, 6-9, 13-20, 22-24, 27-29, 35-38. 41-43, 45,49-53 were rejected under 35 U.S.C. 102(b) as being anticipated by Huber (4,122,157). Applicants respectfully request reconsideration of this rejection in view of the foregoing amendments to the claims and the ensuing discussion.

The Huber reference describes oral tablets having:

> two discrete portions, a rapid release portion and a slow release portion, each portion containing a specific quantity of specially prepared nitrofurantoin. Still more particularly, the present invention relates to a compressed pharmaceutical table...In addition, the present invention relates to a method of treating urinary tract infections in humans which comprises the oral administration of a tablet of the present invention not more than three times daily...[Huber, col. 1, l. 47-67]

Thus, Huber relates to a compressed tablet suitable for oral administration. It was to be formulated for disintegration by the gastrointestinal tract. In contrast, the freeze-dried compositions of applicants' invention are not compressed. They therefore should have lower density than compressed tablets as well as different disintegration and release properties. Nowhere in Huber is there a description or suggestion of pharmaceutical compositions that have been freeze-dried. In view of this distinction, applicants respectfully request reconsideration of the rejection under 35 U.S.C. 102(b).

The Office Action of August 1, 2001 further rejected claims 1, 2, 6, 7, 25 and 53 under 35 U.S.C. 102(b) as being anticipated by Iwata et al. (XP-002162841). Applicants respectfully request reconsideration of this rejection in light of the foregoing amendments to the claims and the ensuing discussion.

Iwata et al. is an abstract of a study relating to a sustained-release double-layered progesterone suppository for luteal-support therapy. While Iwata et al. describes a vaginal suppository, it indicates that the inner layer of the suppository consists of a "stick" containing hydroxypropylcellulose, carbopol and crystalline cellulose as well. Nowhere does Iwata et al. suggest or describe a freeze-dried composition or dosage form. Thus, the claims, as amended, are distinct from the dosage forms set forth in Iwata et al. Applicants therefore respectfully request reconsideration of the rejection under 35 U.S.C. 102(b) in view of Iwata et al.

The Office Action further rejected claims 1-55 under 35 U.S.C. 103(a) as being unpatentable over Huber in view of Morella et al. and Gole et al., in further view of Comte et al. and Saslawski et al. Applicants respectfully request reconsideration of this rejection in light of the foregoing amendments to the claims and the ensuing discussion.

As discussed above, Huber relates to a compressed tablet, which is a relatively dense structure and which was formulated specifically for oral administration and digestion within the stomach and gastrointestinal tract. Morella et al. also relates to an oral tablet for sustained release via stomach digestion. Morella's tablet contains an inner core and an outer coating; the coating is formulated specifically for fast dissolution. Applicants could not find reference within the Morella et al. patent indicating that this outer coating should contain drug or active ingredient. Rather, the sustained release action of the tablet of Morella et al. is due to partial solubility of the core ingredients at high pH, such as that in the stomach. Morella et al. appears to have been cited solely for the proposition that metronidazole can be used in a pharmaceutical composition. Even in combination with Huber, one of ordinary skill in the art would not have reached the compositions of applicants' invention based upon Morella et al.

Nor does Gole et al. compensate for the insufficiencies of the combination of Huber and Morella et al. in directing one of ordinary skill in the art toward the compositions of applicants' invention. Gole et al. relates to a solid freeze-dried dosage form which dissolves quickly [col. 2, l. 39-45 and 54-55] and a method for making such a dosage form. Gole et al. describes homogeneous dosage forms and nowhere suggests or describes the use of such quickly dissolving compositions in combination with another, sustained release layer. Nor does Gole et al. motivate one of ordinary skill in the art to combine its teachings with Huber or Morella et al. in order to reach the compositions of applicants' invention.

First, the Huber and Morella et al. references describe only compressed solid tablets and would not motivate one of ordinary skill in the art to combine these compositions with lyophilized compositions. Second, the problems inherent in freeze-drying would discourage even one of ordinary skill in the art familiar with lyophilization to utilize a multi-layer composition and be able to attain a usable dosage form. Freeze-drying often results in cracking due to stresses during ice crystallization or meltback. One would not expect a composition containing two or more distinct types of compositions in one multilayered unit to achieve a cohesive product. Such a structure would have been expected to crack due to the stresses resulting from different reactions to the lyophilization process. Further, the disparate ingredients might have been expected to have different melting and freezing properties.

Nor would one expect, in light of Gole et al., that a composition containing two freeze-dried layers would result in a dual-rate release composition. Thus, there is no motivation to combine Huber, Morella et al. and Gole et al. in order to produce a composition according to applicants' invention.

Neither the Comte et al. nor the Saslawski et al. reference would have motivated one of ordinary skill in the art to the compositions of applicants' invention. Comte et al. relates to bilayer tablets which may effervesce at varying rates to provide a rapid release and a slower, sustained release. The Saslawski et al. reference relates a bilayer tablet that contains an outer layer which allows immediate release of an active and a second layer containing "a nonbiodegradable, inert porous polymeric matrix in which a second active substance is dispersed" [Saslawski, et al., p. 1 Abstract]. Neither reference suggests or describes a freeze-dried composition nor a combination of any freeze-dried layer with another layer to attain a dual-rate release composition. Applicants therefore request reconsideration of the rejection of the claims under 35 U.S.C. 103(a) over Huber in view of Comte et al. and Saslawski et al. In light of the foregoing discussion, applicants respectfully request reconsideration of the rejections under 35 U.S.C. 103(a) over Huber in view of Morella et al., Gole et al., Comte et al. and Saslawski et al.

In view of the foregoing discussion, applicants respectfully request reconsideration of the rejections set forth in the Office Action of August 1, 2001. An early allowance is earnestly solicited.

Respectfully submitted,

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